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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
FALK, ANNE MARIE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/933,640	MASLIAH ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,27,28,32-37 and 39-43* is/are pending in the application.

4a) Of the above claim(s) *37 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,27,28,32-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed Juned 28, 2007 (hereinafter referred to as "the response") has been entered. Claims 1, 27, 37, and 39-43 have been amended. Claims 14-26, 29-31, and 38 have been cancelled.

Accordingly, Claims 1-13, 27, 28, 32-37, and 39-43 remain pending in the instant application.

The elected invention is drawn to a transgenic mouse comprising, integrated into its genome, a gene encoding human amyloid precursor protein and a gene encoding human α-synuclein.

Claims 37 and 39 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. The election was made without traverse in the response filed May 8, 2006.

Accordingly, Claims 1-13, 27, 28, 32-36, and 40-43 are examined herein.

The objection to Claim 23 under 37 CFR 1.75(c) is withdrawn in view of the cancellation of the claim.

The rejection of Claims 1-13 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn in view of the amendment to Claim 1.

The rejection of Claim 24 under 35 U.S.C. 112, second paragraph, for indefiniteness, is withdrawn in view of the cancellation of the claim.

With regard to the interview request, at page 8 of the response, Applicants are directed to MPEP 408.

Applicants' request for rejoinder between product and process claims, at page 9 of the response, is noted. Applicants allege that Group II encompasses withdrawn process claims which depend from or otherwise include all the limitations of the allowed product claims. Contrary to this assertion, however, the product claims are not currently allowable and therefore the process claims will not be rejoined at this

time. The withdrawn process claims depend from rejected claims. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained.

Claim Objections

Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 is directed to the transgenic mouse of Claim 1, wherein proteins encoded by the first and second transgenic nucleotide sequences are overexpressed as compared to levels of equivalent proteins encoded by a non-transgenic mouse of the same strain. Since Claim 1 is directed to a mouse expressing two human proteins, the mouse of Claim 1 necessarily overexpresses the "proteins encoded by the first and second transgenic nucleotide sequences" as set forth in Claim 1. There are no strains of non-transgenic mice that express human proteins. Therefore, expression of a single protein molecule encoded by the first and second transgenic nucleotide sequences already represents overexpression of the proteins. Claim 1 already includes the limitation that "the first and second transgenic nucleotide sequences are expressed."

Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 28 is directed to the transgenic mouse of Claim 27, wherein proteins encoded by the first and second transgenic nucleotide sequences are overexpressed as compared to a non-transgenic mouse of the same strain. Since Claim 27 is directed to a mouse expressing two human proteins, the mouse of Claim 27 necessarily overexpresses the "proteins encoded by the first and second transgenic nucleotide sequences" as set forth in Claim 27. There are no strains of non-transgenic mice that express human

proteins. Therefore, expression of a single protein molecule encoded by the first transgenic nucleotide sequence accompanied by expression of a single protein molecule encoded by the second transgenic nucleotide sequence already represents overexpression of the proteins. Claim 27 already includes the limitation that "the first and second transgenic nucleotide sequences are expressed."

Double Patenting

Claim 6 is objected to under 37 CFR 1.75 as being a substantial duplicate of Claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims include new matter.

Claim 41 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by the method of Claim 40.

Claim 42 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by propagating the transgenic mice of Claim 41.

Claim 43 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by propagating the transgenic mice of Claim 1.

The claims are product-by-process claims. Claim 41 requires at least one breeding step, whereas Claims 42 and 43 each require at least 2 breeding steps. However, the specification does not contemplate making an inbred transgenic mouse strain by breeding transgenic mice made by the method of Claim 40. Likewise, the specification does not contemplate making an inbred transgenic mouse strain by breeding transgenic mice made by propagating the transgenic mice of Claim 41. Likewise, the specification does not contemplate making an inbred transgenic mouse by breeding transgenic mice made by propagating the transgenic mice of Claim 1.

As noted at page 4 of the Office Action of 1/29/07, Claims 42 and 43 are directed to a very broad scope of combination transgenics because the claims do not specify a breeding partner, and therefore the mice of the invention may be bred to any other transgenic mouse to produce combination transgenics that are neither described nor enabled by the instant specification, for reasons of record. As currently amended, Claims 41-43 cover this broad scope of combination transgenics.

At page 9 of the response, Applicants assert that support for mouse strains made from transgenic mice of this invention can be found in paragraph [0032] of U.S. Patent Application Publication No. 20030056231 (the pre-grant publication of this application). However, paragraph [0032] only contemplates combining known strains of mice to develop bigenic strains that most closely mimic the disease state of interest. The cited section does not contemplate the particular multiple breeding steps as recited in the instant claims, nor does it contemplate making an inbred transgenic mouse by breeding transgenic mice made by the method of Claim 40. Clearly, the specification does not contemplate the product-by-process as now claimed. Thus, there is no support for the inbred transgenic mouse strains of

the product-by-process claims. Given the product-by-process format of the claims, the claims cover inbred transgenic mice having any transgene whatsoever or any number of multiple transgenes. Since the breeding partners are not specified, the transgenic mouse of Claim 40, which has only a single allele of each of the genes recited in the claim, may be mated with any other transgenic mouse to produce any type of transgenic mouse, having one or any number of different transgenes. Such a mouse may or may not comprise one or both of the transgenes recited in Claim 40. Clearly, the specification does not contemplate the breeding processes recited in the claims and the multitude of inbred mouse strains that may be generated by such breeding.

Since the as-filed specification does not contemplate the inbred transgenic mouse strains of the present product-by-process claims, nor the process used to make said strains, such a claim raises an issue of new matter. Claims directed to subject matter not disclosed in the originally filed specification cannot be introduced after the application filing date. Applicants have not pointed to appropriate support for the newly added claim limitations in the as-filed specification.

Thus, the claims include new matter.

Enablement

Claims 27, 28, 32-36, and 40-43 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Actions of 8/2/06 and 1/29/07, and the Advisory Action of 6/14/07, because the specification, while being enabling for a transgenic mouse comprising: a first transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding the wild-type human amyloid precursor protein, 751 amino acid isoform (hAPP751), operably linked to a neuron-specific promoter; and a second transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding wild-type human α-synuclein operably linked to a neuron-specific promoter; wherein the first and second transgenic nucleotide sequences are expressed, and

wherein said transgenic mouse develops amyloidosis, neurofibrillary tangles, and intraneuronal accumulation of α-synuclein,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants are reminded that the above-indicated scope of enablement is not meant to suggest specific claim language and that proper support in the as-filed specification for any claim terminology introduced by amendment is always required.

Claim 27 has been amended to remove the phenotype from the claim, thereby broadening the scope of the claim. Furthermore, Claim 27 continues to cover transgenic mice having any mutant form of human α-synuclein, when only mice having the wild-type transgene are enabled by the instant specification, for reasons of record. Such claims are broader than the indicated scope of enablement. No arguments are provided to address this broader scope.

As noted in the Advisory Action of 6/14/07, Claim 40 covers mice having any phenotype whatsoever or no transgene-dependent phenotype at all. Thus, Claim 40 and its dependent claims are broader in scope than the scope of enablement. No arguments are provided to address this broader scope.

As noted at page 4 of the Office Action of 1/29/07, Claims 42 and 43 are directed to a very broad scope of combination transgenics because the claims do not specify a breeding partner, and therefore the mice of the invention may be bred to any other transgenic mouse to produce combination transgenics that are neither described nor enabled by the instant specification, for reasons of record. As currently amended, Claims 41-43 cover this broad scope of combination transgenics.

Therefore, the rejection is maintained.

The following claim would be allowable:

27. A transgenic mouse comprising:

a first transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding the wild-type human amyloid precursor protein, 751 amino acid isoform (hAPP751), operably linked to a platelet-derived growth factor-β (PDGF-β) promoter operably linked to a simian virus 40 (SV40) intron; and

a second transgenic nucleotide sequence, integrated into the genome of said mouse, comprising a sequence encoding the wild-type human (h) α-synuclein operably linked to a PDGF-β promoter operably linked to an SV40 intron;

wherein the first and second transgenic nucleotide sequences are expressed, and as a result of expression of the hAPP751 and (h) α-synuclein, said transgenic mouse develops amyloidosis, neurofibrillary tangles, and intraneuronal accumulation of (h) α-synuclein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 and 32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13 are indefinite in their recitation of "a wild type human (h) α-synuclein" because use of the indefinite article "a" instead of the definite article "the" seems to indicate that there would be multiple forms of the wild-type human α-synuclein when there should be only one wild-type human α-synuclein. As noted at the bottom of page 2 of the Advisory Action of 6/14/07, Claim 1 should be amended to recite the definite article "the" rather than the indefinite article "a" before the two instances of "wild type."

Claim 7 is indefinite in its recitation of "said PDGF-β promoter" because the term lacks proper antecedent basis. Claim 6, from which Claim 7, depends recites that the "first promoter comprises a PDGF-β promoter." Thus, the phrase "said PDGF-β promoter" as set forth in Claim 7, clearly refers to the "first promoter" as set forth in Claim 6. However, Claim 7 further provides that said PDGF-β promoter is operably linked to the second transgenic nucleotide sequence. This conflicts with the limitations of Claim 1, from which Claim 7 ultimately depends, which require that the first promoter be operably linked to the first transgenic nucleotide sequence, not the second transgenic nucleotide sequence as set forth in Claim 7. Thus, the limitations of Claim 7 conflict with the limitations of Claim 1 and "said PDGF-β promoter" lacks proper antecedent basis.

Claims 32-36 are indefinite in their recitation of "neurodegenerative disease" because the term lacks antecedent basis.

Claim 36 is indefinite in its recitation of the parenthetical subject matter "($p<0.05$)" and "(having only one of either the first or the second transgene)" because it is unclear if the material in parentheses is an actual claim limitation. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Boggio et al. (1998, J. Exp. Med. 188(3): 589-596).

Claim 41 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by the method of Claim 40. Claim 42 is directed to an inbred transgenic mouse strain made by breeding

transgenic mice made by propagating the transgenic mice of Claim 41. Claim 43 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by propagating the transgenic mice of Claim 1. The claims are product-by-process claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. See MPEP 2113. Thus, the claims read on a wide variety of inbred transgenic mice having any transgene, as well as mice having any combination of any number of transgenes.

Boggio et al. (1998) disclose BALB/c HER-2/*neu* transgenic mice (abstract and page 590, column 1, paragraph 3). BALB/c is an inbred strain of mouse. The reference further discloses FVB mice carrying the HER-2/*neu* protooncogene (abstract and page 590, column 1, paragraph 3). As the reference discloses, FVB mice are an inbred mouse strain (page 590, column 1, paragraph 3). Since the claims do not specify any particular breeding partner, but instead only require "breeding transgenic mice made by the method of claim 40" or "breeding transgenic mice made by propagating the transgenic mice of claim 41" or "breeding transgenic mice made by propagating the transgenic mice of claim 1," the breeding or propagating step may involve any other transgenic mouse in addition to the transgenic mouse made by the method of Claim 40. The mouse made by the method of Claim 40 would have one hAPP751 transgene and one human α-synuclein transgene and could be on any genetic background, including FVB, which is a common strain used for producing transgenics. On breeding such a mouse with an FVB HER-2/*neu* transgenic mouse one would obtain FVB progeny having the HER-2/*neu* transgene, but no hAPP751 transgene and no human α-synuclein transgene (these are the mice disclosed in the reference and therefore the claim covers the mice of the reference), as well as wild-type mice, mice having all three transgenes, mice having any combination of two of the transgenes, and singly transgenic mice having any one of the three transgenes. Thus, the claims cover the FVB HER-2/*neu* mice disclosed in the reference, as these mice can be produced by the methods recited in the claims.

Thus, the claimed invention is disclosed in the prior art.

Claims 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Geng et al. (1998, PNAS 95: 10055-10060).

Claim 41 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by the method of Claim 40. Claim 42 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by propagating the transgenic mice of Claim 41. Claim 43 is directed to an inbred transgenic mouse strain made by breeding transgenic mice made by propagating the transgenic mice of Claim 1. The claims are product-by-process claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. See MPEP 2113. Thus, the claims read on a wide variety of inbred transgenic mice having any transgene, as well as mice having any combination of any number of transgenes.

Geng et al. (1998) disclose FVB GAD65 transgenic mice (abstract and page 10056, column 1, paragraph 1). FVB is an inbred strain of mouse. Since the claims do not specify any particular breeding partner, but instead only require "breeding transgenic mice made by the method of claim 40" or "breeding transgenic mice made by propagating the transgenic mice of claim 41" or "breeding transgenic mice made by propagating the transgenic mice of claim 1," the breeding or propagating step may involve any transgenic mouse in addition to the transgenic mouse made by the method of Claim 40. The mouse made by the method of Claim 40 would have one hAPP751 transgene and one human α-synuclein transgene and could be on any genetic background, including FVB, which is a common strain used for producing transgenics. On breeding such a mouse with an FVB GAD65 transgenic mouse one would obtain FVB progeny having the GAD65 transgene, but no hAPP751 transgene and no human α-synuclein transgene (these are the mice disclosed in the reference and therefore the claim covers the mice of the reference), as

well as wild-type mice, mice having all three transgenes, mice having any combination of two of the transgenes, and singly transgenic mice having any one of the three transgenes. Thus, the claims cover the FVB GAD65 mice disclosed in the reference, as these mice can be produced by the methods recited in the claims.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Claims 1-5, 8-11, and 13 would be allowable if amended to overcome the rejection under 35 U.S.C. 112, second paragraph. Claim 1 should be amended to recite "the wild-type human (h) α-synuclein" instead of "a wild-type human (h) α-synuclein."

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632